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| 09/961,128 | 09/21/2001 | Marianne Kearney | 49138 (71417) | 4197 |

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| EXAMINER | |
|---|---|
| QIAN, CELINE X | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/961,128 | KEARNEY ET AL. | |
| | Examiner | Art Unit | |
| | Celine X Qian | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *4,5,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-17 are pending in the application. Claims 4, 5, 13 and 14 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-3, 6-12 and 15-17 are currently under examination.

This Office Action is in response to the amendment filed on 12/29/03.

### *Response to Amendment*

The objection to drawings is maintained for reasons discussed below.

The rejection of claims 1-3, 6-12 and 15-17 under 35 U.S.C.112 2nd paragraph is maintained for same reasons set forth of the record mailed on 7/28/2003 and further discussed below.

Claims 1-3, 6-12 and 15-17 stand rejected under 35 U.S.C.103(a) for reasons discussed below.

### *Response to Arguments*

#### *Drawing*

In response to the drawing objection, Applicants proposed to add a Figure 1 legend. However, this legend is not present in the attached Replacement Figures. The drawings filed on 9/21/2001 contain two sets of drawings. It is unclear which one is for official record. The objection will be withdrawn when Applicants clarify these matters and amend the description of the drawings in the specification to replace "Figure 1" with "Figures 1A-1C."

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-12, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6-12, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to determine the ability of a gene encoding for an endothelial cell mitogen to produce a biologically active endothelial cell mitogen protein or the ability of a first plasmid DNA construct containing a gene encoding for an endothelial cell mitogen to produce a bioactive endothelial cell mitogen protein as compared to the ability of a second plasmid DNA construct containing a gene encoding for an endothelial cell mitogen to produce a bioactive endothelial cell mitogen protein.

In response to this rejection, applicants argue that the amended claims overcome this rejection. This argument has been fully considered but deemed unpersuasive. As indicated in the previous office action, the method claims are required to refer back to the preamble so that there should have no gap between the steps and what the method is going to achieve. Since the claims are drawn to a method for testing a plasmid containing a gene encoding for an endothelial cell mitogen for the ability to produce a biologically active endothelial cell mitogen protein or a method for evaluating the ability of a first plasmid DNA construct containing a gene encoding for an endothelial cell mitogen to produce a bioactive endothelial cell mitogen protein as compared to the ability of a second plasmid DNA construct containing a gene encoding for an endothelial cell mitogen to produce a bioactive endothelial cell mitogen protein, such methods should comprise a step such as "wherein the level of cell survival indicate said plasmid produces

an active endothelial cell mitogen" to make the method complete. The present claims do not have a step that refers back to the preamble of the method, thus the method is not complete. Therefore, the rejection is maintained.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 103***

In response to the rejection of claims 1-3, 7-12, 16 and 17 under 35 U.S.C.103(a) over Sugihara in view of Buttke, Applicants argue that the cited references fail to provide a motivation to combine and result in the claimed invention. Applicants argue that the transfection assay method described by Sugihara et al. involves stable rather than transient transfection as claimed. Applicants further argue that Sugihara et al. describe a cell mitogenic assay using thymidine incorporation as a means for measuring cell proliferation rather than cell survival as claimed. Furthermore, Applicants argue that Buttke et al. teach away from Sugihara by emphasizing a marked preference for the need for both tests (thymidine incorporation and MTS) as a means of measuring and comparing two different cell parameters. Finally, Applicants argue that neither reference teaches testing a plasmid for use in human gene therapy treatment.

In response to the rejection of claims 6 and 15 under 35 U.S.C. 103 (a) over Sugihara in view of Buttke and Delli-Bovi, Applicants argue that Delli-Bovi et al. do not remedy the deficiency as discussed above, Applicants thus conclude that the invention is not obvious.

Applicants' argument has been fully considered and deemed partially persuasive. The claims are rejected as discussed below.

Claims 1-3, 6-12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara et al., in view of Buttke et al. and Breier et al.

The teaching of Sugihara et al. was discussed in the Office Action mailed on 7/28/03. However, Sugihara et al. do not teach using Cos-1 cell line as host cells expressing the endothelial mitogen protein and the conditioned media are collected from transiently transfected host cell line.

The teaching of Buttke et al. was discussed in the Office Action mailed on 7/28/03. Buttke et al. further teach that MTS assay measures both mitogen induced cell proliferation and cell viability. Buttke et al. demonstrate that cell proliferation measured by thymidine incorporation correlated with MTS assay during the initial period, whereas MTS assay is more indicative of the number of cell viable when DNA synthesis declined (see page 238, 1st col.). Buttke et al. thus conclude that it is of particular interest to compare MTS-formazan production with thymidine uptake in cell culture (see page 238, 1st col., 1st paragraph, lines 14-15). Moreover, Buttke et al. show that MTS and labeled thymidine can be simultaneously added to cell cultures with each having little effect on the other. Since growth factors may either enhance cell viability or induce proliferation, Buttke et al. indicate that the ability to measure both MTS reduction and thymidine uptake in a single culture will be useful in studies pertaining to the isolation or characterization of novel growth factors (see page 239, 2nd col., last paragraph).

Breier et al. teach that conditioned media following transient transfection of expression vector comprising VEGF cDNA to Cos-1 cells are collected and assayed for mitogenic activity on bovine aortic endothelial cells (see page 524, 2nd col., 2nd paragraph, and page 522, Material and Methods, 1st paragraph).

It would have been obvious to one of ordinary skill of art to develop a method of testing the biological activity of a endothelial cell mitogen protein such as VEGF by measuring the

survival rate of endothelial cells incubating with conditioned media collected from host cells transfected with vector encoding a endothelial cell mitogen based on the teaching of Sugihara et al (claims 1-3, 7-12, 16 and 17). Methods of measuring cell survival are well known in the art. Such methods include MTS/formazan assay taught by Buttke et al. One of ordinary skilled in the art would have been motivated to use MTS/formazan assay to measure cell survival because of the teaching of Burttke et al., who teach that MTS measures a cell survival, rather than cell proliferation as compared to thymidine incorporation. In addition, MTS/formazan and labeled thymidine can be added to cell culture simultaneously, then both parameters can be measured at the same time to determine whether a given factor affect proliferation or cell survival. Given the advantage of this assay, it would have been obvious to one of ordinary skill of art to use it in the mitogen assay taught by Sugihara et al. to measure cell survival. Although the assay taught by Sugihara et al uses conditioned media from a stabled transfected cell line, one of ordinary skill in the art would recognize that conditioned media from host cells transiently transfected with a plasmid encoding the mitogen protein can also accomplish this task because method of transient transfection and stable transfection can be used interchangeably for the purpose of a mitogenic assay. For example, Breier et al. teach a method for assaying mitogenic activity of VEGF on bovine aortic endothelial cells, in which it uses conditioned media from Cos-1 cells transiently transfected with expression vector expressing VEGF. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation of success to develop a method of testing the biological activity of a endothelial cell mitogen protein by transiently transfecting the expression vector to a host cell line, incubating endothelial cell with the conditioned media from the transiently transfected host cell line, and determine cell

survival by MTS assay. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

It would also have been obvious to one of ordinary skill of art to used the method taught by Sugihara et al. and using Cos-1 cell as host cell for expressing endothelial cell mitogen protein because both NIH3T3 cells and Cos-1 cells are widely used in transfection experiment and expressing a protein of interest (claims 6 and 15). The ordinary artisan would have been motivated to use either Cos-1 or NIH3T3 as host cells because both Sugihara et al. and Breier et al. teach that conditioned media from either cell line transfected with endothelial mitogen protein promotes endothelial cell growth. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation of success to use Cos-1 cells to express a biological active endothelial mitogen protein. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

In response to Applicant's argument regarding the combined references do not teach testing an expression vector before gene therapy, Applicant is reminded that the intended use of the plasmid is not a limitation of the claims. The intended use of the plasmid does not affect/change the claimed method steps, thus the references still render the claims obvious even they do not teach the intended use of the plasmid.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.